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(71) Applicant: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(72) Inventors: **FERTIG, Georg**; Wolfbauerweg 6, 82377 Penzberg (DE). **HERTING, Frank**; Frauenschuhstrasse 38, 82377 Penzberg (DE). **KUBBIES, Manfred**; Glaswandstrasse 7c, 82377 Penzberg (DE). **LIMBERG, Anja**; Würmseestrasse 58, 81476 München (DE). **REIFF, Ulrike**; Weidenweg 6, 82377 Penzberg (DE). **WEIDNER, Michael**; Ludwig-März-Strasse 39a, 82377 Penzberg (DE).

(74) Agent: **SCHREINER, Siegfried**; Roche Diagnostics GmbH, Patent Department (TR-E), Postfach 11 52, 82372 Penzberg (DE).

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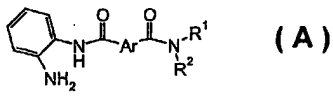
(54) Title: NEW MONO-ACYLATED O-PHENYLENDIAMINES DERIVATIVES



(A)

(57) Abstract: Objects of the present invention are new mono-acylated o-phenylendiamines derivatives of formula (A) wherein Ar is thiophen-2,5-diyl, pyridine-2,5-diyl, pyridine-5,2-diyl, pyridine-2,6-diyl, pyridine-2,4-diyl or 1,4-phenylene, R^1, R^2 independently from each other represent hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{3-12}-cycloalkyl, the alkyl, alkenyl, alkynyl and cycloalkyl groups being optionally mono or multiple substituted by hydroxy, halogen, C_{3-12}-cycloalkyl, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$, or alternatively R^1 is hydrogen, and R^2 is hydroxyl, alkoxy, C_2.C_{12}-alkenyloxy or phenoxy, which phenoxy group is optionally substituted with methyl, methoxy, halogen, nitro, cyano, trifluoromethyl, ethenyl or $-C(O)-O-CH_3$, provided that if R^2 is hydroxy, Ar is not thiophen-2,5-diyl; and R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl, or wherein R^3 and R^4 together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom, and pharmaceutically acceptable salts thereof, as well as processes for the manufacturing of these compounds, pharmaceutical compositions containing such compounds and their use in the manufacture of drugs for the treatment of diseases such as cancer.

WO 2004/069803 A2

New mono-acylated o-phenylendiamines derivatives

Objects of the present invention are new mono-acylated o-phenylendiamines derivatives and pharmaceutically acceptable salts thereof. The invention also relates to processes for the manufacturing of these compounds of formula I, to pharmaceutical compositions containing such compounds and to their use in the manufacture of drugs for the treatment of diseases such as cancer.

Cancer is one of the major causes of death, exceeding heart and cerebrovascular diseases, and so many studies have been conducted with enormous expense and time to overcome cancer. However, in spite of a variety of therapies such as surgical operation, radiation therapy and chemotherapy, there is still a great need for improved anticancer therapeutics. Among these therapies, chemotherapy is one of the main areas for cancer treatment. Most drugs show their effect by affecting mainly DNA to express their cytotoxicity and then, in consequence injuring tumor cells. However, lacking selectivity, they do not sufficiently differentiate between tumor cells and normal cells, and therefore, adverse reactions expressed in normal cells have limited their use in therapy. Up to now, no satisfactory drugs have been discovered, and thus an anticancer drug with reduced toxicity, better tolerability and a high therapeutic effect is very much desired.

The compounds according to this invention are inhibitors of histone deacetylase (HDAC) and therefore show antiproliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion.

Transcriptional regulation is a major event in cell differentiation, proliferation, and apoptosis. Transcriptional activation of a set of genes determines cell destination and for this reason transcription is tightly regulated by a variety of factors. One of its regulatory mechanisms involved in the process is an alteration in the tertiary structure of DNA, which affects transcription by modulating the accessibility of transcription factors to their target DNA segments. Nucleosomal integrity is regulated by the acetylation status of the core histones. In a hypoacetylated state, nucleosomes are tightly compacted and thus are nonpermissive for transcription. On the other hand, nucleosomes are relaxed by acetylation of the core histones, with the result being permissiveness to transcription. The acetylation status of the

histones is governed by the balance of the activities of histone acetyl transferase (HAT) and histone deacetylase (HDAC). Recently, HDAC inhibitors have been found to arrest growth and induce apoptosis in several types of cancer cells, including colon cancer cells, T-cell lymphoma cells, and erythroleukemic cells. Given that apoptosis is a crucial factor for cancer progression, HDAC inhibitors are promising reagents for cancer therapy as effective inducers of apoptosis (Koyama, Y., et al., Blood 96 (2000) 1490-1495).

The compounds of the present invention surprisingly show low toxicity, together with a potent anti-proliferative and cell differentiation activity characterized by enhanced acetylation due to inhibition of HDAC.

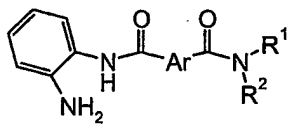
EP-A 0 847 992 describes monoacylated o-phenylendiamine derivatives as cell differentiation inducers. The same type of compounds is also the subject of EP-A 0 242 851. The compounds described in these applications are almost exclusively o-phenylene derivatives monoacylated with derivatives of benzoic acid. However, there is still a need to provide compounds with improved properties such as increased tolerability, less toxicity and less side effects.

Monoacylated o-phenylendiamines are known in the art as precursors for the preparation of the corresponding benzimidazoles, such preparation methods are e.g. described in DE-A 2 062 265; FR 2 167 954; Rastogi, R., and Sharma, S., Indian J. Chem., Sect. B, 21B (5) (1982) 485-487; Moll, R., et al., Z. Chem. 17 (1977) 133-134; and Hassan, H., et al., Indian J. Chem. 39B (2000) 764-768.

It has been found that the compounds of the present invention are HDAC inhibitors which have anti-proliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion. These compounds are therefore useful for the treatment of diseases such as cancer in humans or animals. Examples of tumors which may be treated, but are not limited to, colon cancers, breast carcinoma (including advanced breast cancer), lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), prostate cancer including advanced disease, pancreatic cancers, hematopoetic tumors of lymphoid lineage (e.g. acute lymphotic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MSD), tumors of mesenchymal origin, melanomas, teratocarcinomas,

neuroblastomas, gliomas, benign tumors of the skin (e.g. keratoacanthomas), kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

The present invention concerns new compounds of the general formula A



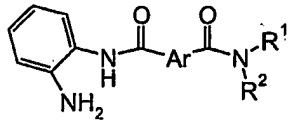
A

wherein

Ar	is thiophen-2,5-diyl, pyridine-2,5-diyl, pyridine-5,2-diyl, pyridine-2,6-diyl, pyridine-2,4-diyl or 1,4-phenylene,
R^1, R^2	independently from each other represent hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{3-12}-cycloalkyl, the alkyl, alkenyl, alkynyl and cycloalkyl groups being optionally mono or multiple substituted by hydroxy, halogen, C_{3-12}-cycloalkyl, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or -NR^3R^4, or alternatively
R^1	is hydrogen, and
R^2	is hydroxyl, alkoxy, C_2-C_{12}-alkenyloxy or phenoxy, which phenoxy group is optionally substituted with methyl, methoxy, halogen, nitro, cyano, trifluoromethyl, ethenyl or –C(O)-O-CH_3, provided that if R^2 is hydroxy, Ar is not thiophen-2,5-diyl; and
R^3 and R^4	independently from each other represent hydrogen or C_{1-6}-alkyl, or wherein
R^3 and R^4	together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom,

and pharmaceutically acceptable salts thereof.

Especially preferred are the compounds of formula I



I

wherein

Ar	is thiophen-2,5-diyl, pyridine-2,5-diyl, pyridine-5,2-diyl or 1,4-phenylene,
R^1, R^2	independently from each other represent hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{3-12}-cycloalkyl, the alkyl, alkenyl, alkynyl and cycloalkyl groups being optionally mono or multiple substituted by hydroxy, halogen, C_{3-12}-cycloalkyl, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or -NR^3R^4,
R^3 and R^4	independently from each other represent hydrogen or C_{1-6}-alkyl, or wherein
R^3 and R^4	together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom,

and pharmaceutically acceptable salts thereof.

The present invention also encompasses pharmaceutically acceptable salts or prodrugs of the compounds of formula A or formula I as well as the use of these compounds, salts and prodrugs to produce pharmaceutical agents.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

The term "C_1-C_{12}-alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 12 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl, pentyl, hexyl, heptyl and the like. The term "C_1-C_6 alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms. The alkyl group may optionally be mono or multiple substituted by hydroxy, halogen, C_{3-12}-cycloalkyl, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or -NR^3R^4. Examples of substituted alkyl residues are for example trifluoromethyl, pentafluoroethyl, 2-dimethylamino-ethyl, 2-diethylamino-ethyl, 2-dibutylamino-ethyl, 2-diisopropylamino-ethyl, 2-methoxy-ethyl, 2-ethoxy-ethyl, 2-propyloxy-ethyl, 3-dimethylamino-propyl, 3-diethylamino-propyl, 3-dibutylamino-propyl, 3-diisopropylamino-propyl, 3-methoxy-propyl, 3-ethoxy-propyl, 3-propyloxy-propyl, 2-acetylamino-ethyl, 3-acetylamino-proyl, 2-methoxy-1-methyl-ethyl (in its (R), (S)

and (R,S) form), cyclopropylmethyl, 3-dimethylamino-2,2-dimethylpropyl, 3-(2-oxo-pyrrolidin-1-yl)-propyl or 2-(2-oxo-pyrrolidin-1-yl)-ethyl.

The term "alkoxy" denotes a group wherein the alkyl residue is as defined above, and which is attached via an oxygen atom.

The term "alkylsulfanyl" denotes a group wherein alkyl residue is as defined above, and which is attached via an sulfur atom.

The term "acyloxy" denotes a group alkyl-C(O)-O-, wherein alkyl residue is as defined above.

The term "alkoxycarbonyl" denotes a group alkyl-O-C(O)-, wherein alkyl residue is as defined above.

The term " acyl" denotes a group alkyl-C(O)-, wherein alkyl residue is as defined above.

The term "C_2-C_{12}-alkenyl" refers to an unsaturated alkyl group having 2 to 12 carbon atoms and at least one double bond, preferably allyl or pentadienyl.

The term "C_2-C_{12}-alkynyl" refers to an unsaturated alkyl group having 2 to 12 carbon atoms and at least one triple bond, such as prop-2-ynyl, preferably propargyl.

The term "C_2-C_{12}-alkenyloxy" denotes a group wherein the alkenyl residue is as defined above, and which is attached via an oxygen atom, preferably allyloxy.

The term "C_3-C_{12}-cycloalkyl" as used in the present invention denotes saturated carbocyclic rings with 3 to 12 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term " together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom " refers to heterocycles such as pyrrolidinone-1-yl or piperidinone-1-yl.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid, cyclohexanesulfamic acid and the like.

Compounds of the present invention can contain one or several chiral centres and can then be present in a racemic or in an optically active form. The racemates can be separated according to known methods into the enantiomers. Preferably diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid. Furthermore, the racemic compounds can be separated into their enantiomers by chromatography on an analytical, semipreparative or preparative scale using suitable optically active stationary phases with suitable eluents. Suitable optically active stationary phases include, but are not limited to, silica (e.g. ChiraSper,Merck; Chiralpak OT/OP, Baker), cellulose esters or carbamates (e.g. Chiracel OB/OY, Baker) or others (e.g. Crownpak, Daicel or Chiracel OJ-R, Baker).

Enantiomers, diastereoisomers and racemates of formula A or I and their pharmaceutically acceptable salts are also part of the invention.

Preferred groups of compounds of formula I or A are compounds, wherein R^1 is hydrogen or alkyl, and R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined above;

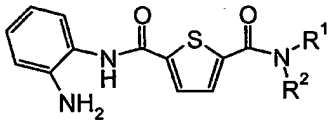
compounds of formula I or A, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl;

compounds, wherein R^1 is hydrogen and R^2 is unsubstituted straight or branched C_{1-12}-alkyl or alkyl mono or multiple substituted by alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-;

compounds of formula I or A, wherein R^1 is hydrogen and R^2 is C_{1-12}-alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl; and

compounds of formula I or A according to claim 1, wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom.

Preferred are the compounds of formula I, wherein Ar is thiophen-2,5-diyl of the formula I-A



I-A,

wherein

R^1 is hydrogen or C_{1-6}-alkyl; and

R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined above.

Examples of such compounds are

ex. no.	compound
1-19	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(butyl-methyl-amide),
1-34	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-diethylamide,
1-36	Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-prop-2-ynyl-amide),
1-37	thiophene-2,5-dicarboxylic acid 2-(allyl-methyl-amide) 5-[(2-amino-phenyl)-amide],
1-38	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylaminoethyl)-ethyl-amide],
1-39	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-dipropylamide,
1-40	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-pentyl-amide),

1-41 thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diethylaminoethyl)-methyl-amide],

1-42 thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[bis-(2-methoxy-ethyl)-amide],

1-44 thiophene-2,5-dicarboxylic acid 2-amide 5-[(2-amino-phenyl)-amide].

Further preferred are the compounds of formula I or A or I-A, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl.

Such compounds are for example

ex. no. Compound

1-30 thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-prop-2-ynylamide,

1-32 thiophene-2,5-dicarboxylic acid 2-allylamide 5-[(2-amino-phenyl)-amide].

Further preferred are compounds of formula I or A or I-A, wherein R^1 is hydrogen and R^2 is unsubstituted straight or branched C_{1-12}-alkyl or alkyl mono or multiple substituted by alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-.

Examples of such compounds are

ex. no. Compound

1-1 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-butyl)-amide],

1-6 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-hexyl)-amide],

1-9 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-methoxy-propyl)-amide],

1-10 Thiophene-2,5-dicarboxylic acid 2-[(2-acetylaminoethyl)-amide] 5-[(2-amino-phenyl)-amide],

1-11 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-ethyl-hexyl)-amide],

1-13 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1,5-dimethyl-hexyl)-amide],

1-15 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methoxy-1-methyl-ethyl)-amide],

1-20 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-pentylamide,

1-21 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-butylamide,

1-23 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-ethoxy-propyl)-amide],

1-24 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-sec-butylamide,

1-25 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-heptylamide,

1-26 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-nonylamide,

1-27 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-octylamide,

1-28 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-heptyl)-amide],

1-29 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(isobutylamide),

1-31 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-propylamide;

1-35 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methyl-butyl)-amide].

Further preferred are compounds of formula I or A or I-A wherein R^1 is hydrogen and R^2 is C_{1-12}-alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl;

Examples of such compounds are

ex. no. Compound

1-2 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-diethylamino-1-methyl-butyl)-amide],

1-3 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-diethylamino-propyl)-amide],

1-4 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dibutylamino-propyl)-amide],

1-5 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dimethylaminopropyl)-amide],

1-8 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-diisopropylaminoethyl)-amide],

1-17 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dimethylamino-2,2-dimethylpropyl)-amide],

1-18 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylaminoethyl)-amide].

Further preferred are compounds of formula I or A or I-A wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom.

An example of such a compound is

1-22 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-{[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide}.

Further preferred are the compounds of formula I or A or I-A, wherein R^1 is hydrogen or alkyl and R^2 is cycloalkyl or alkyl substituted by cycloalkyl. Such compounds are for example

1-7 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cycloheptylamide,

1-12 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclooctylamide,

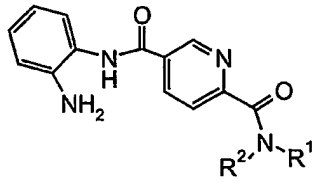
1-14 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclopentylamide,

1-33 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclobutylamide,

1-43 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(cyclopropylmethyl-propyl-amide),

1-16 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclopropylmethyl-amide.

Further preferred are the compounds of formula I or A wherein Ar is pyridine-2,5-diyl of formula I-B



I-B,

wherein

R^1 is hydrogen or alkyl; and

R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined above.

Examples of such a compounds are

2-3 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-(butyl-methyl-amide),

2-14 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-dipropylamide,

2-16 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-(methyl-pentyl-amide),

2-17 Pyridine-2,5-dicarboxylic acid 2-(allyl-methyl-amide) 5-[(2-amino-phenyl)-amide],

2-18 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[bis-(2-methoxy-ethyl)-amide],

2-19 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-diethylaminoethyl)-methyl-amide].

Further preferred are the compounds of formula I or A or I-B, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl.

An example of such a compound is

2-4 Pyridine-2,5-dicarboxylic acid 2-allylamide 5-[(2-amino-phenyl)-amide].

Further preferred are compounds of formula I or A or I-B, wherein R^1 is hydrogen and R^2 is unsubstituted straight or branched C_{1-12}-alkyl or alkyl mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-.

Examples of such compounds are

2-2 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-hexylamide,

2-7 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-methoxy-ethyl)-amide],

2-8 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(3-butoxy-propyl)-amide],

2-9 {[5-(2-amino-phenylcarbamoyl)-pyridine-2-carbonyl]-amino}-acetic acid methyl ester,

2-10 3-{[5-(2-amino-phenylcarbamoyl)-pyridine-2-carbonyl]-amino}-propionic acid tert-butyl ester,

2-11 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2,2,3,3,3-pentafluoro-propyl)-amide],

2-12 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2,2,3,3,4,4,4-heptafluoro-butyl)-amide],

2-13 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(1,5-dimethyl-hexyl)-amide],

2-15 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(1-methyl-hexyl)-amide],

2-20 Pyridine-2,5-dicarboxylic acid 2-[(2-acetylaminoethyl)-amide] 5-[(2-amino-phenyl)-amide].

Further preferred are compounds of formula I or A or I-B wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl.

Examples of such compounds are

2-1 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-diisopropylamino-ethyl)-amide],

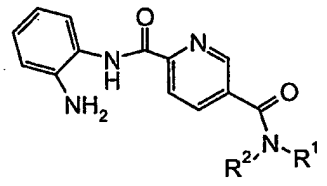
2-6 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(3-dibutylamino-propyl)-amide].

Further preferred are the compounds of formula I or A or I-B, wherein R^1 is hydrogen and R^2 is cycloalkyl.

An example of such a compound is

2-5 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-cyclooctylamide.

Further preferred are compounds of formula I or A wherein Ar signifies pyridine-5,2-diyl of formula I-C



I-C,

wherein

R1 is hydrogen or alkyl; and

R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined above.

Examples of such compounds are

3-23 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(butyl-methyl-amide),

3-24 pyridine-2,5-dicarboxylic acid 5-(allyl-methyl-amide) 2-[(2-amino-phenyl)-amide],

3-25 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-prop-2-ynyl-amide),

3-26 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[bis-(2-methoxyethyl)-amide],

3-27 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-pentyl-amide),

3-29 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-dipropylamide,

3-30 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diethylaminoethyl)-methyl-amide].

Further preferred are the compounds of formula I or A or I-C, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl.

An example of such compounds is

3-2 pyridine-2,5-dicarboxylic acid 5-allylamide 2-[(2-amino-phenyl)-amide].

Further preferred are compounds of formula I or A or I-C, wherein R^1 is hydrogen and R^2 is unsubstituted alkyl or alkyl mono or multiple substituted by hydroxy, halogen, , alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-.

Examples of such compounds are

3-3 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-hexylamide,

3-6 pyridine-2,5-dicarboxylic acid 5-[(2-acetylamino-ethyl)-amide] 2-[(2-amino-phenyl)-amide],

3-7 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2,2,3,3,3-pentafluoro-propyl)-amide],

3-8 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2,2,3,3,4,4,4-heptafluoro-butyl)-amide],

3-9 3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-butyric acid ethyl ester,

3-10 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-hydroxy-propyl)-amide],

3-11 2-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-3-methyl-butyric acid methyl ester,

3-12 3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-propionic acid ethyl ester,

3-13 {[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-acetic acid methyl ester,

3-14 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methoxy-ethyl)-amide],

3-15 2-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-4-methylsulfanyl-butyric acid methyl ester,

3-16 3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-propionic acid tert-butyl ester,

3-17 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2,3-dihydroxy-propyl)-amide],

3-18 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-butoxy-propyl)-amide],

3-21 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-sec-butylamide,

3-22 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1,5-dimethyl-hexyl)-amide],

3-31 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-hexyl)-amide].

Further preferred are compounds of formula I or A or I-C wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl.

Examples of such compounds are

3-1 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diisopropylamino-ethyl)-amide],

3-5 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylamino-ethyl)-amide],

3-19 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-diethylamino-1-methyl-butyl)-amide],

3-20 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dibutylamino-propyl)-amide].

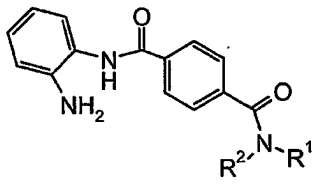
Further preferred are the compounds of formula I or A or I-C, wherein R^1 is hydrogen or alkyl and R^2 is cycloalkyl.

Example of such compounds are

3-4 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclooctylamide,

3-28 pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(cyclopropylmethyl-propyl-amide).

Further preferred are compounds of formula I or A, wherein Ar signifies 1,4-phenylene, namely compounds of formula I-D



I-D,

wherein

R^1 is hydrogen or alkyl; and

R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined above.

An example of such a compound is

4-13 N-(2-amino-phenyl)-N'-butyl-N'-methyl-terephthalamide.

Further preferred are the compounds of formula I or A or I-D, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl.

Such compounds are for example

4-11 N-allyl-N'-(2-amino-phenyl)-terephthalamide.

Further preferred are compounds of formula I or A or I-D, wherein R^1 is hydrogen and R^2 is unsubstituted straight or branched alkyl or alkyl mono or multiple substituted by , alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-.

Examples of such compounds are

4-5 N-(2-amino-phenyl)-N'-(2-methoxy-1-methyl-ethyl)-terephthalamide,
4-7 N-(2-amino-phenyl)-N'-(3-ethoxy-propyl)-terephthalamide,
4-12 N-(2-amino-phenyl)-N'-butyl-terephthalamide.

Further preferred are compounds of formula I or A or I-D wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl.

Examples of such compounds are

4-1 N-(2-amino-phenyl)-N'-(2-diisopropylamino-ethyl)-terephthalamide,
4-2 N-(2-amino-phenyl)-N'-(3-dibutylamino-propyl)-terephthalamide,
4-3 N-(2-amino-phenyl)-N'-(4-diethylamino-1-methyl-butyl)-terephthalamide,
4-4 N-(2-amino-phenyl)-N'-(3-diethylamino-propyl)-terephthalamide,
4-8 N-(2-amino-phenyl)-N'-(2-dimethylamino-ethyl)-terephthalamide,
4-10 N-(2-amino-phenyl)-N'-(3-dimethylamino-2,2-dimethyl-propyl)-terephthalamide.

Further preferred are compounds of formula I or A or I-D, wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom.

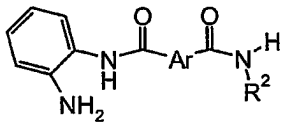
An example of such a compound is

4-9 N-(2-amino-phenyl)-N'-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-terephthalamide.

Further preferred are the compounds of formula I or A or I-D, wherein R^1 is hydrogen, alkyl or alkenyl and R^2 is cycloalkyl or alkyl substituted by cycloalkyl. Such a compound is for example

4-6 N-(2-amino-phenyl)-N'-cyclopropylmethyl-terephthalamide.

Another embodiment of the invention are compounds of the formula I-E



I-E

wherein

Ar is thiophen-2,5-diyl, pyridine-2,5-diyl, pyridine-2,6-diyl, pyridine-2,4-diyl, pyridine-5,2-diyl or 1,4-phenylene; and

R^2 represents hydroxyl, alkoxy, C_2-C_{12}-alkenyloxy or phenoxy, provided that if R^2 is hydroxy, Ar is not thiophen-2,5-diyl.

Examples of such compounds are

5-1 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methoxy-amide),

5-2 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(ethoxy-amide),

5-3 Thiophene-2,5-dicarboxylic acid 2-(allyloxy-amide) 5-[(2-amino-phenyl)-amide],

5-4 Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(phenoxy-amide),

5-5 Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-hydroxyamide,

5-6 Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-hydroxyamide,

5-7 Pyridine-2,6-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 6-hydroxyamide,

5-8 Pyridine-2,4-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 4-hydroxyamide.

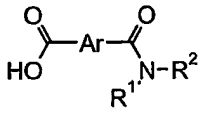
Still another embodiment of the present invention are the compounds of formula I or A,

Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(tert-butoxy-amide),
Pyridine-2,5-dicarboxylic acid 2-(allyl-cyclopentyl-amide) 5-[(2-amino-phenyl)-amide],
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-(cyclopropylmethyl-propyl-amide),
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-sec-butylamide,
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-hydroxy-ethyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-{[2-(2-hydroxy-ethoxy)-ethyl]-amide},
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-cyclohexylmethyl-2-hydroxy-ethyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-hydroxy-butyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-hydroxymethyl-2-methyl-butyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-hydroxy-cyclohexyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-({2-[bis-(2-hydroxy-ethyl)-amino]-ethyl}-amide),
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-dimethylamino-ethyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylamino-ethyl)-ethyl-amide].

An aromatic dicarboxylic acid derivative of the formula I or A, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare an aromatic dicarboxylic acid derivative of the formula I or A, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated, Ar, R^1 and R^2 have the meanings defined above. Starting

materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

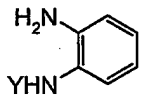
(a) One preferred method for the production of compounds of the formula I or A involves the reaction of compounds of the formula II



II

wherein Ar, R^1 and R^2 are as defined above;

with a compound of the formula III



III

wherein Y represents hydrogen or a suitable amino protecting group.

Protection groups for the amino group are known from peptide chemistry, such protecting groups are for example, benzyloxycarbonyl (cleavage by hydrogenation or hydrobromic acid in acetic acid), t-butoxycarbonyl (cleavage by strong acids, such as, trifluoroacetic acid neat or in dichloromethane, or HCL in dioxane), 9-fluorenmethoxycarbonyl (cleavage by secondary amines, such as, piperidine).

If R^2 in formula A is OH, this hydroxyl group might bear a protecting group for the reaction of HNR^1R^2 with compound V or VI as described below. A protection group for the hydroxyl group is, among others, benzyl ether which can be cleaved by hydrogenation. Some of the O-protected HNR^1R^2 groups such as O-benzylhydroxylamine are commercially available.

This reaction typically involves a two-step one-pot procedure. In the first step, the carboxylate of the formula II is activated by reaction of the compound in an inert

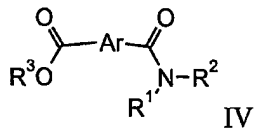
solvent or diluent, for example, in dichloromethane, dioxane, or tetrahydrofuran, in the presence of an activating agent.

A suitable reactive derivative of an acid is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride or oxalic acid dichloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol; an active ester formed by the reaction of the acid and N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N-3-dimethylaminopropyl-N-ethylcarbodiimid or dicyclohexylcarbodiimide; or the product of the reaction of the acid with N,N'-carbonyldiimidazole; or the product of the reaction of the acid and uroniumsalts such as O-(1H-benzotriazol-1-yl)-N,N,N',N',-tetramethyluronium tetrafluoroborate; or the product of the reaction of the acid and phosphorus based reagents, e.g. bis-(2-oxo-3-oxazolidinyl)-phosphorylchloride. The reaction is carried out between -30°C and 60°C, conveniently at or below 0°C.

In the second step, compound III is added to the solution containing the activated acid. If Y is a protecting group it finally has to be cleaved (methods see above) to yield compound I. In order to obtain the compounds wherein R^2 is a hydroxyl group, amino- and hydroxyl protecting groups might both be present in the molecule. In this case the hydroxyl protecting group has to be cleaved before the amino protecting group using the methods described above.

These methods are well known to those skilled in the art. In principle, all methods for the synthesis of amides as used in peptide chemistry as described in e.g. "Methoden der organischen Chemie (Houben-Weyl)" Band XV/1 and XV/2 are also applicable. Monoacylation of unprotected phenylene diamine is described in EP0974576.

(b) Compounds of formula II can be prepared by hydrolysis from compounds of formula IV

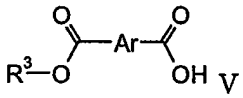


IV

wherein R^3 is alkyl or aralkyl, preferably methyl, ethyl, t-butyl, benzyl.

The conditions under which the cleavage is carried out depend on the nature of the group R^3. When R^3 is an alkyl group such as methyl or ethyl, the reaction is carried out in the presence of a base, for example, lithium hydroxide, sodium hydroxide, or potassium hydroxide in an inert solvent or diluent, for example, in MeOH, ethanol, dioxane, THF, water. When R^3 is the t-butyl group, the reaction is carried out in the presence of an acid, for example, a solution of hydrochloric acid in an inert solvent such as diethyl ether or dioxane, or trifluoroacetic acid in dichloromethane. When R^3 is the benzyl group, the reaction is carried out by hydrogenolysis in the presence of a noble metal catalyst such as palladium or platinum on a suitable carrier, such as carbon. The methods used for the hydrolysis of the ester are of course dependent on the nature of the residues R^1 and R^2.

(c) Compounds of formula IV are prepared from compounds of the formula V wherein Ar and R^3 have the meaning defined above.



V

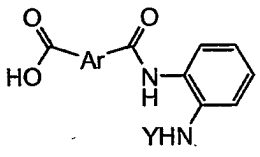
This reaction typically involves a two-step one-pot procedure. In the first step, the carboxylate of the formula V is activated using the methods described under (a).

In the second step, an amine of the formula HNR^1R^2 in which R^1 and R^2 have the meaning defined above is added to the solution, at the temperature used for the activation, and the temperature is slowly adjusted to ambient temperature. An appropriate scavenger base like e.g. triethylamine, or diisopropylethlyamine may be added to the reaction mixture. These methods are well known to those skilled in the art. In principle, all methods for the synthesis of amides as used in peptide

chemistry as described in e.g. "Methoden der organischen Chemie (Houben-Weyl)" Band XV/1 and XV/2 are also applicable.

(d) There are quite a few compounds of formula V described in the literature. For example, the terephthalic monomethylester is described in e.g. Holba, V., et al., Z. Phys. Chem. 262 (1981) 445-448. It is also commercially available. Pyridine-2,5-dicarboxylic acid 5-methyl ester is described in e.g. WO 93/21146. Thiophene-2,5-dicarboxylic acid monomethyl ester is described in e.g. US 2,680,731. These monoesters are usually prepared by selective saponification of the diester, but other method may be useful as well and are well known to those skilled in the art.

(e) Another preferred method for the production of compounds of the formula I or A involves the reaction of compounds of the formula VI



VI

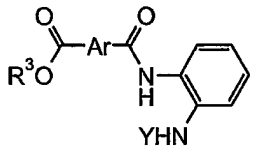
wherein Ar has the meaning defined above and Y is suitable protecting group as described in (a)

with an amine of the formula HNR^1R^2 in which R^1 and R^2 have the meaning defined hereinbefore.

This reaction typically involves a two-step one-pot procedure and is carried out according to the methods described in (a).

Finally Y has to be cleaved by methods as described above to give compound I. As mentioned above, if both the amino- and hydroxyl protecting groups are present in the molecule, the hydroxyl protecting group should be cleaved before the amino protecting group.

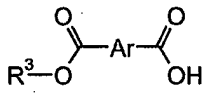
(f) Compounds of the formula VI are prepared by hydrolysis as described in (b) from compounds of the formula VII



VII

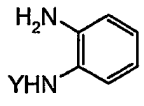
wherein R^3 and Y have the meaning defined above.

g) Compounds of formula VII are prepared from compounds of the formula V wherein A and R^3 have the meaning defined hereinbefore



V

with a compound of the formula III



III

wherein Y represents a suitable protecting group as described in (a).

This reaction typically involves a two-step one-pot procedure as described in (a).

The compounds of formula I or A and their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found the they possess antiproliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion, these compounds are useful for the treatment of diseases such as cancer in humans or animals.

The activity of the compounds according to this invention as HDAC inhibitors is demonstrated using a cellular acetylation assay. Therein acetylation of histones is monitored in PC3 cells. High acetylation correlates with inhibition of histone deacetylase by compounds. Cell viability is monitored in parallel to estimate the cytotoxicity of compounds.

PC3 cells, a human prostate carcinoma cell line, are seeded as 1800 cells per well of a 384-well microtiterplate in RPMI 1640 (including 5% FCS, 2mM glutamine and pen / strep).

After 48 h at 37 °C pre-diluted compounds are added to a final concentration of 1 uM. Compounds are pre-diluted in dimethyl sulfoxide (DMSO) resulting in a final concentration of DMSO of 0.5 % per well.

After 24 h incubation cell viability is determined by adding cell proliferation reagent WST-1 (Roche Molecular Biochemicals). Another 60 min later the optical density (OD) is measured (450 nm versus 690 nm).

After measurement the cell layer is prepared for the ELISA reaction. Medium is aspirated and cells are fixed in ethanol at –20 °C for 60 min. After washing with PBS / Tween the blocking solution (PBS/ 5% FCS / Tween) is added and the cell layer is washed again. Antibodies against acetylated histone H3 or H4 (rabbit polyklonal IgG, Upstate Biotechnologie) are added at a dilution of 1:200 for 60 min at 37 °C. As a second antibody goat anti rabbit IgG (H+L) humanIgG adsorbed-HRP conjugate (Dako) is used (1:2000 diluted). Cells are washed 3 times and the peroxidase substrate ABTS is allowed to react for 30-60 min at 37 °C. The OD is measured at 405 nm.

The percentage of acetylation is calculated after substraction of blank O.D.s:

$$\frac{\frac{\text{mean O.D. acetylation}}{\text{mean O.D. DMSO control}}}{\frac{\text{mean O.D. WSTI}}{\text{mean O.D. DMSO control}}} \times 100\%$$

Example No.	Compound Name	cell acetylation (PC3, 1 µM) [% of control]
	Reference Compound 4-acetylamino-N-(2-amino-phenyl)-benzamide	152
1-1	Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-butyl)-amide]	137.2

Example No.	Compound Name	cell acetylation (PC3, 1 μM) [% of control]
1-4	Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dibutylamino-propyl)-amide]	195.7
1-6	Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl.hexyl)-amide]	122.9
1-17	Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dimethylamino-2,2-dimethylpropyl)-amide]	149.8
1-18	Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylaminoethyl)-amide]	233.9
1-19	Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(butyl-methyl-amide)	118.8
1-24	Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-sec-butylamide	211.2
1-35	Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methyl-butyl)-amide]	135.4
1-44	Thiophene-2,5-dicarboxylic acid 2-amide 5-[(2-amino-phenyl)-amide]	185.6
2-1	Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-diisopropylamino-ethyl)-amide]	206.6
3-1	Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diisopropylamino-ethyl)-amide]	244.8
3-5	Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylamino-ethyl)-amide]	154.6
3-9	3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-butyric acid ethyl ester	211.6
3-20	Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dibutylamino-propyl)-amide]	223.8
4-1	N-(2-amino-phenyl)-N'-(2-diisopropylamino-ethyl)-terephthalamide	399.3

The new compounds of formula I or A and the pharmaceutically acceptable salts thereof can be used as medicaments, i.e. in form of pharmaceutical preparations. The pharmaceutical preparations can be administered enterally or parenterally in a

liquid or solid form. In this connection all the usual forms of administration come into consideration such as for example tablets, capsules, coated tablets, syrups, solutions, suspension, suppositories etc. Water which contains additives such as stabilizers, solubilizers and buffers that are usual in injection solutions is preferably used as the injection medium.

Such additives are e.g. tartrate and citrate buffer, ethanol, complexing agents (such as ethylenediaminetetraacetic acid and non-toxic salts thereof), high-molecular polymers (such as liquid polyethylene glycols) to regulate viscosity. Liquid carrier substances for injection solutions have to be sterile and are preferably dispensed into ampoules. Solid carrier substances are e.g. starch, lactose, mannitol, methylcellulose, talcum, highly dispersed silicic acids, higher molecular fatty acids (such as stearic acid), gelatins, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high-molecular polymers (such as polyethylene glycols); suitable preparations for oral application can optionally also contain flavourings and sweeteners.

Medicaments containing a compound of formula I or A or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I or A and/or their pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of formula I or A as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based on their HDAC inhibition and therefore of antiproliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion, these compounds are useful for the treatment of diseases such as cancer in humans or animals and for the production of corresponding medicaments.

The dosage depends on various factors such as manner of administration, species, age and/or individual state of health. The doses to be administered daily are about 5-400 mg/kg, preferably 10-100 mg/kg and can be taken singly or distributed over several administrations.

The invention will now be illustrated in the following examples in which, unless otherwise stated:

i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) column chromatography (by the flash procedure) and high pressure liquid chromatography (HPLC) were performed on Merck Kieselgel silica or Merck Lichroprep RP-18 reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Kofler hot plate apparatus;

(vi) the structures of the products of the formula I or A were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques (Micromass Platform II machine using APCI or Micromass Platform ZMD using electrospray);

(vii) intermediates were not generally fully characterized and purity was assessed by thin layer chromatography;

(viii) the following abbreviations have been used:

DMF	N,N-dimethylformamide;
DMSO	dimethylsulphoxide;
THF	tetrahydrofuran;
MeOH	methanol;
HCl	hydrochloric acid;
NaH	sodium hydride

CH_2Cl_2	dichloromethane;
H_2SO_4	sulphuric acid
sat.	saturated
sol.	solution
h	hour
d	days
rt	room temperature
eq	equivalent

Example 1

Preparation of compounds of formula I-A

Step 1: **5-(2-tert-Butoxycarbonylamino-phenylcarbamoyl)-thiophene-2-carboxylic acid methyl ester**

Under an argon atmosphere 21.0g (129mmol) carbonyldiimidazol was added to a solution of 24.1g (129mmol) thiophene-2,5-dicarboxylic acid monomethyl ester in 600ml THF. After 2h at rt 26.9g (129mmol) (2-amino-phenyl)-carbamic acid tert-butyl ester were added and the reaction mixture was stirred for further 4h at rt. The solvent was evaporated and the residue dissolved in 500ml ethyl acetate. The organic phase was washed three times with 100ml saturated aqueous $NaHCO_3$ solution, twice with 80ml water and was dried over sodium sulfate. The solvent was removed down to 80ml when crystallization started. After 12h the crystalls were filtered off and washed with little ice-cold t-butyl methyl ether and cold heptane. Drying under high vacuum yielded 38.9g (103.4mmol) 5-(2-tert-butoxycarbonyl-amino-phenylcarbamoyl)-thiophene-2-carbox-ylic acid methyl ester, ^{1}H-NMR (D_6-DMSO) δ = 1.45 (s, 9H), 3.87 (s, 3H), 7.14 (m, 1H), 7.22 (m, 1H), 7.46 (m, 1H), 7.59 (m, 1H), 7.89 (m, 1H), 7.96 (m, 1H), 8.73 (br, 1H), 10.02 (s, 1H).

Step 2: **5-(2-tert-Butoxycarbonylamino-phenylcarbamoyl)-thiophene-2-carboxylic acid**

To a suspension of 18.5g (50mmol) 5-(2-tert-Butoxycarbonylamino-phenyl-carbamoyl)-thiophene-2-carboxylic acid methyl ester in 500ml MeOH was added within 20 minutes a solution of 5.6g (100mmol) potassium hydroxide in 100ml water. The reaction mixture was stirred at room temperature for 2d. The MeOH was evaporated and the remaining aqueous solution was extracted three times with

ethylacetate and acidified with a 3N aqueous HCl solution. The precipitation was filtered off, washed with water and dried at 45°C in high vacuum to yield 14.5g (40mmol) 5-(2-tert-butoxycarbonylamino-phenylcarbamoyl)-thiophene-2-carboxylic acid. , ^{1}H-NMR (D_6-DMSO) δ = 1.45 (s, 9H), 7.14 (m, 1H), 7.22 (m, 1H), 7.46 (m, 1H), 7.59 (m, 1H), 7.90 (m, 2H), 8.72 (s, 1H), 9.99 (s, 1H), 13.54 (s, 1H).

Step 3: **(2-{[5-(1-Methyl-butylcarbamoyl)-thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester**

To a solution of 4.4g (12.1mmol) 5-(2-tert-butoxycarbonylamino-phenylcarbamoyl)-thiophene-2-carboxylic acid in 80ml THF were added 2.2g (13.6mmol) carbonyldiimidazol. The reaction mixture was stirred at 45°C for 1h and then cooled to rt. After addition of 1.05g (12mmol) 2-pentylamine the reaction mixture was kept at rt for 12h. The solvent was evaporated and the residue was dissolved in 150ml CH_2Cl_2. The solution was washed twice with 150ml water each and dried over magnesium sulfate. The solvent was evaporated and the residue was washed with diethyl ether to yield (2-{[5-(1-methyl-butylcarbamoyl)-thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester as a white solid, mp. 183°C.

Step 4: **Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-butyl)-amide] (compound 1-1)**

To a solution of 3.3g (7.65mmol) (2-{[5-(1-methyl-butylcarbamoyl)-thiophene-2-carbonyl]-amino}-phenyl)-carbamic acid tert-butyl ester in 80ml MeOH were added 16ml of a 4M solution of HCl in dioxane under ice cooling. After the solution was stirred for 3h at rt the solvent was evaporated. To the residue were added 50ml dichloromethane and 50ml of a 1M aqueous solution of $NaHCO_3$. After stirring at rt for 30 minutes the precipitation was filtered off, washed with water and dried to yield 2.3g (6.9mmol) thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-butyl)-amide], mp. 192°C, calculated MW (M+H) 332.14, found (M+H) 332.2; ^{1}H-NMR (400 MHz, $(CH_3)_2SO$): δ = 9.77 (s, 1H), 8.33 (d, J = 8.6 Hz, 1H), 7.92 (m, 1H), 7.78 (m, 1H), 7.13 (m, 1H), 6.99 (m, 1H), 6.78 (m, 1H), 6.59 (m, 1H), 4.96 (s, 2H), 3.97 (m, 1H), 1.57-1.39 (m, 2H), 1.36-1.26 (m, 2H), 1.14 (d, J = 6.6 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H).

In analogy to steps 1 to 4 of Example 1 using the appropriate starting material the following compounds where prepared:

no.	name	calc. MW (M+H)	found MW (M+H)
1-2	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-diethylamino-1-methyl-butyl)-amide]; H-NMR (400 MHz, $(CH_3)_2SO$): δ = 9.75 (s, 1H), 8.33 (d, J = 8.6 Hz, 1H), 7.91 (m, 1H), 7.78 (m, 1H), 7.13 (m, 1H), 6.98 (m, 1H), 6.78 (m, 1H), 6.59 (m, 1H), 4.93 (s, 2H), 3.97 (m, 1H), 2.46-2.33 (m, 6H), 1.53-1.38 (m, 4H), 1.15 (d, J = 6.6 Hz, 3H), 0.93 (t, J = 7.1 Hz, 6H);	403.22	403.1
1-3	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-diethylamino-propyl)-amide]; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ = 9.76 (s, 1H), 8.65 (t, J = 5.05 Hz, 1H), 7.92 (m, 1H), 7.71 (m, 1H), 7.13 (m, 1H), 6.99 (m, 1H), 6.78 (m, 1H), 6.59 (m, 1H), 4.93 (s, 2H), 3.27 (m, 2H), 2.46 (q, J = 7.07 Hz, 4H), 2.43 (t, J = 7.83, 2H), 1.64 (m, 2H), 0.95 (t, J = 7.33, 6H);	375.19	375.1
1-4	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dibutylamino-propyl)-amide];	431.25	431.1
1-5	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dimethylamino-propyl)-amide];	347.15	347.3
1-6	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl.hexyl)-amide]; ^{1}H-NMR (400 MHz, $(CH_3)_2SO$): δ = 9.75 (s, 1H), 8.31 (d, J = 8.6 Hz, 1H), 7.91 (m, 1H), 7.78 (m, 1H), 7.14 (m, 1H), 6.98 (m, 1H), 6.78 (m, 1H), 6.59 (m, 1H), 4.93 (s, 2H), 3.95 (m, 1H), 1.57-1.41 (m, 2H), 1.34-1.22 (m, 6H), 1.14 (d, J = 6.6 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H);	360.17	360.3
1-7	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cycloheptylamide;	358.16	358.2
1-8	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-diisopropylamino-ethyl)-amide];	389.20	389.3

no.	name	calc. MW (M+H)	found MW (M+H)
1-9	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-methoxy-propyl)-amide];	334.12	334.2
1-10	thiophene-2,5-dicarboxylic acid 2-[(2-acetylamino-ethyl)-amide] 5-[(2-amino-phenyl)-amide];	347.12	347.2
1-11	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-ethyl-hexyl)-amide];	374.19	374.2
1-12	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclooctylamide;	372.17	372.2
1-13	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1,5-dimethyl-hexyl)-amide];	374.19	374.2
1-14	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclopentylamide;	330.13	330.2
1-15	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methoxy-1-methyl-ethyl)-amide];	334.12	334.2
1-16	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclopropylmethyl-amide;	316.11	316.2
1-17	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dimethylamino-2,2-dimethyl-propyl)-amide];	375.19	375.2
1-18	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylamino-ethyl)-amide]; ^{1}H-NMR (400 MHz, $(CH_3)_2SO$): δ = 9.84 (s, 1H), 8.84 (t, 5.6 Hz, 1H), 7.96 (m, 1H), 7.74 (m, 1H), 7.12 (m, 1H), 6.99 (m, 1H), 6.78 (m, 1H), 6.59 (m, 1H), 4.96 (s, 2H), 3.57 (m, 2H), 3.19 (m, 2H), 2.80 (s, 6H);	333.14	333.2
1-19	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(butyl-methyl-amide);	332.14	332.3
1-20	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-pentylamide;	332.14	332.2
1-21	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-butylamide;	318.13	318.2
1-22	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-{[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide};	387.15	387.1

no.	name	calc. MW (M+H)	found MW (M+H)
1-23	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-ethoxy-propyl)-amide];	348.14	348.2
1-24	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-sec-butylamide; ^{1}H-NMR (400 MHz, $(CH_3)_2SO$): δ = 9.77 (s, 1H), 8.32 (d, J = 8.1 Hz, 1H), 7.92 (m, 1H), 7.80 (m, 1H), 7.13 (m, 1H), 6.98 (m, 1H), 6.78 (m, 1H), 6.59 (m, 1H), 4.94 (s, 2H), 3.87 (m, 1H), 1.59-1.44 (m, 2H), 1.15 (d, J = 6.6 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H);	318.13	318.2
1-25	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-heptylamide;	360.17	360.2
1-26	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-nonylamide;	388.21	388.3
1-27	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-octylamide;	374.19	374.3
1-28	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-heptyl)-amide];	374.19	374.3
1-29	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(isobutyl-amide);	318.13	318.2
1-30	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-prop-2-ynylamide;	300.08	300.1
1-31	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-propylamide;	304.11	304.2
1-32	thiophene-2,5-dicarboxylic acid 2-allylamide 5-[(2-amino-phenyl)-amide];	302.10	302.2
1-33	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclobutylamide;	316.11	316.2
1-34	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-diethylamide;	318.13	318.2

no.	name	calc. MW (M+H)	found MW (M+H)
1-35	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methyl-butyl)-amide]; ^{1}H-NMR (400 MHz, $(CH_3)_2SO$): δ = 9.79 (s, 1H), 8.61 (t, 5.8 Hz, 1H), 7.93 (m, 1H), 7.77 (m, 1H), 7.12 (m, 1H), 6.99 (m, 1H), 6.78 (m, 1H), 6.59 (m, 1H), 4.95 (s, 2H), 3.21-3.15 (m, 1H), 3.08-3.02 (m, 1H), 1.67-1.57 (m, 1H), 1.46-1.36 (m, 1H), 1.17-1.07 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H);	332.14	332.2
1-36	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-prop-2-ynyl-amide);	314.10	314.1
1-37	thiophene-2,5-dicarboxylic acid 2-(allyl-methyl-amide) 5-[(2-amino-phenyl)-amide];	316.11	316.3
1-38	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylamino-ethyl)-ethyl-amide];	361.17	361.2
1-39	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-dipropylamide;	346.16	346.2
1-40	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-pentyl-amide);	346.16	346.2
1-41	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diethylamino-ethyl)-methyl-amide];	375.19	375.3
1-42	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[bis-(2-methoxy-ethyl)-amide];	378.15	378.1
1-43	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(cyclopropylmethyl-propyl-amide);	358.16	358.2
1-44	thiophene-2,5-dicarboxylic acid 2-amide 5-[(2-amino-phenyl)-amide].	262.07	262.2

Example 2

Preparation of compounds of formula I-B

Step 1: **6-(2-Diisopropylamino-ethylcarbamoyl)-nicotinic acid methyl ester**

A suspension of 1.1g (5mmol) potassium 5-methoxycarbonyl-pyridine-2-carboxylate, 0.9ml (12mmol) thionyl chloride and 0.1ml DMF in 5ml dichloroethane was heated at reflux for 2h. To the reaction mixture 5ml CH_2Cl_2 were added and the solvent was evaporated. This procedure was repeated three times. The residue was suspended in 5ml CH_2Cl_2 and a solution of 9.95ml (5.5mmol) 2-diisopropylaminoethylamine, 0.97ml (7mmol) triethylamine, 0.1ml DMF in 5ml CH_2Cl_2 was added under ice-cooling. After stirring for 12h at rt the organic phase was extracted with water, 5% citric acid and aqueous $NaHCO_3$ and dried over magnesium sulfate. After evaporation of the solvent the residue was subjected to silica gel chromatography (20% MeOH and 1% triethylamine in ethyl acetate) to yield 1.15g (3.7mmol) 6-(2-diisopropylamino-ethylcarbamoyl)-nicotinic acid methyl ester; exact MW [M+H] calcd: 308.20; MW found [M+H]: 308.20.

Step 2: **6-(2-Diisopropylamino-ethylcarbamoyl)-nicotinic acid**

To a solution of 1100mg (3.6mmol) 6-(2-diisopropylamino-ethylcarbamoyl)-nicotinic acid methyl ester in 10ml THF and 3.0ml MeOH was added 3.6ml of an 2N aqueous NaOH solution. After 4h at rt the solvent was evaporated. The residue was acidified with 1N HCl, filtered off and washed with water to give 936mg (3.2mmol) 6-(2-diisopropylamino-ethylcarbamoyl)-nicotinic acid; ; exact MW [M+H] calc'd: 294.18; MW found [M+H]: 209.15.

Step 3: **Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-diisopropylamino-ethyl)-amide] compound (2-1)**

A solution of 936mg (3.2mmol) 6-(2-diisopropylamino-ethylcarbamoyl)-nicotinic acid and 518mg (3.2mmol) carbonyldiimidazol in 8ml THF was heated at 45°C for 1h and then cooled to rt. 1.38g (12.8mmol) phenylenediamine and 0.5ml (6.4mmol) trifluoroacetic acid were added and stirred for 20h at rt. The solvent was evaporated and aqueous ammonia solution was added to the residue. The aqueous phase was extracted with CH_2Cl_2 and the solvent was evaporated from the combined organic phases. The residue was subjected silica gel chromatography

(ethyl acetate then 20% MeOH and 1% triethylamine in ethyl acetate) to yield 404mg (1.06mmol) pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-diisopropylamino-ethyl)-amide]; exact MW [M+H] calc'd: 384.24; MW found [M+H]: 384.23.

The compounds listed below have been prepared according to the method described in example 2 steps 1 to 3.

no.	name	calc. MW (M+H)	found MW (M+H)
2-1	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-diisopropylamino-ethyl)-amide]; ^{1}H-NMR (400 MHz, $(CH_3)_2SO$): δ = 9.93 (s, 1H), 9.16 (m, 1H), 8.84 (t, J = 5.8 Hz, 1H), 8.50 (m, 1H), 8.15 (m, 1H), 7.17 (m, 1H), 6.99 (m, 1H), 6.78 (m, 1H), 6.59 (m, 1H), 5.2 (s, 2H), 3.29 (m, 2H), 3.00 (m, 2H), 2.58 (t, J = 7.3 Hz, 2H), 0.99 (d, J = 6.6 Hz, 12H);	384.24	384.2
2-2	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-hexylamide;	341.20	341.2
2-3	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-(butyl-methyl-amide);	327.18	327.2
2-4	pyridine-2,5-dicarboxylic acid 2-allylamide 5-[(2-amino-phenyl)-amide];	297.14	297.2
2-5	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-cyclooctylamide;	367.21	367.2
2-6	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(3-dibutylamino-propyl)-amide];	426.29	426.3
2-7	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-methoxy-ethyl)-amide];	315.15	315.1
2-8	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(3-butoxy-propyl)-amide];	371.21	371.3
2-9	{[5-(2-amino-phenylcarbamoyl)-pyridine-2-carbonyl]-amino}-acetic acid methyl ester;	329.12	329.1
2-10	3-{[5-(2-amino-phenylcarbamoyl)-pyridine-2-carbonyl]-amino}-propionic acid tert-butyl ester;	385.19	385.3
2-11	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-	389.10	389.1

no.	name	calc. MW (M+H)	found MW (M+H)
	amide] 2-[(2,2,3,3,3-pentafluoro-propyl)-amide];		
2-12	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2,2,3,3,4,4,4-heptafluoro-butyl)-amide];	439.10	439.1
2-13	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(1,5-dimethyl-hexyl)-amide];	369.23	369.3
2-14	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-dipropylamide;	341.20	341.3
2-15	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(1-methyl-hexyl)-amide];	355.21	355.4
2-16	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-(methyl-pentyl-amide);	341.20	341.2
2-17	pyridine-2,5-dicarboxylic acid 2-(allyl-methyl-amide) 5-[(2-amino-phenyl)-amide];	311.15	311.3
2-18	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[bis-(2-methoxy-ethyl)-amide];	373.19	373.3
2-19	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-diethylamino-ethyl)-methyl-amide];	370.22	370.4
2-20	pyridine-2,5-dicarboxylic acid 2-[(2-acetylamino-ethyl)-amide] 5-[(2-amino-phenyl)-amide];	342.16	342.1
2-21	pyridine-2,5-dicarboxylic acid 2-(allyl-cyclopentyl-amide) 5-[(2-amino-phenyl)-amide];	365,45	365,3
2-22	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-(cyclopropylmethyl-propyl-amide);	353,44	353,3
2-23	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-sec-butylamide;	313,38	313,23
2-24	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-dimethylamino-ethyl)-amide].	328,39	328,16

Example 3

Preparation of compounds of formula I-C

In an analogous manner to that described in the example 1, and using known methods as described in the literature (e.g. in standard works such as Houben-Weyl, "Methoden der Organischen Chemie, Georg Thieme Verlag", Stuttgart; Organic

Reactions, John Wiley & Sons, Inc., New York) the following compounds are prepared:

no.	name	calc. MW (M+H)	found MW (M+H)
3-1	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diisopropylamino-ethyl)-amide]; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ = 10.1 (s, 1H), 9.09 (m, 1H), 8.77 (t, J = 5.3 Hz, 1H), 8.41 (m, 1H), 8.22 (m, 1H), 7.47 (m, 1H), 6.97 (m, 1H), 6.83 (m, 1H), 6.65 (m, 1H), 4.92 (s, 2H), 3.27-3.23 (m, 2H), 2.99 (m, 2H), 2.56 (t, J = 7.3 Hz, 2H), 0.99 (d, J = 6.6 Hz, 12H);	384.24	384.2
3-2	pyridine-2,5-dicarboxylic acid 5-allylamide 2-[(2-amino-phenyl)-amide];	297.14	297.2
3-3	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-hexylamide;	341.20	341.3
3-4	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclooctylamide;	367.21	367.3
3-5	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylamino-ethyl)-amide]; ^{1}H-NMR (400 MHz, $(CH_3)_2SO$): δ = 10.11 (s, 1H), 9.09 (m, 1H), 8.77 (t, J = 5.3 Hz, 1H), 8.41 (m, 1H), 8.22 (m, 1H), 7.48 (m, 1H), 6.97 (m, 1H), 6.83 (m, 1H), 6.66 (m, 1H), 4.91 (s, 2H), 3.41 (m, 2H), 2.44 (t, J = 6.8 Hz, 2H), 2.20 (s, 6H);	328.18	328.2
3-6	pyridine-2,5-dicarboxylic acid 5-[(2-acetylamino-ethyl)-amide] 2-[(2-amino-phenyl)-amide];	342.16	342.2
3-7	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2,2,3,3,3-pentafluoro-propyl)-amide];	389.10	389.1
3-8	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2,2,3,3,4,4,4-heptafluoro-butyl)-amide];	439.10	439.1
3-9	3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-butyric acid ethyl ester;	371.17	371.2
3-10	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-hydroxy-propyl)-amide];	315.15	315.2

no.	name	calc. MW (M+H)	found MW (M+H)
3-11	2-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-3-methyl-butyric acid methyl ester;	371.17	371.2
3-12	3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-propionic acid ethyl ester;	357.16	357.1
3-13	{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-acetic acid methyl ester;	329.12	329.1
3-14	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methoxy-ethyl)-amide];	315.15	315.1
3-15	2-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-4-methylsulfanyl-butyric acid methyl ester;	403.14	403.1
3-16	3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-propionic acid tert-butyl ester;	385.19	385.3
3-17	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2,3-dihydroxy-propyl)-amide];	331.14	331.2
3-18	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-butoxy-propyl)-amide];	371.21	371.3
3-19	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-diethylamino-1-methyl-butyl)-amide];	398.26	398.3
3-20	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dibutylamino-propyl)-amide];	426.29	426.3
3-21	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-sec-butylamide;	313.17	313.2
3-22	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1,5-dimethyl-hexyl)-amide];	369.23	369.3
3-23	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(butyl-methyl-amide);	327.18	327.3
3-24	pyridine-2,5-dicarboxylic acid 5-(allyl-methyl-amide) 2-[(2-amino-phenyl)-amide];	311.15	311.3
3-25	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-prop-2-ynyl-amide);	309.14	309.1
3-26	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[bis-(2-methoxy-ethyl)-amide];	373.19	373.2

no.	name	calc. MW (M+H)	found MW (M+H)
3-27	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-pentyl-amide);	341.20	341.2
3-28	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(cyclopropylmethyl-propyl-amide);	353.20	353.2
3-29	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-dipropylamide;	341.20	341.3
3-30	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diethylamino-ethyl)-methyl-amide];	370.22	370.4
3-31	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-hexyl)-amide];	355.21	355.3
3-32	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-hydroxy-ethyl)-amide];	301,32	301,13
3-33	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-{[2-(2-hydroxy-ethoxy)-ethyl]-amide};	345,38	345,13
3-34	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-cyclohexylmethyl-2-hydroxy-ethyl)-amide];	397,5	397,15
3-35	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-hydroxy-butyl)-amide];	329,38	329,11
3-36	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-hydroxymethyl-2-methyl-butyl)-amide];	357,43	357,15
3-37	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-hydroxy-cyclohexyl)-amide];	355,42	355,13
3-38	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-({2-[bis-(2-hydroxy-ethyl)-amino]-ethyl}-amide);	388,45	388,2
3-39	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylamino-ethyl)-ethyl-amide].	356,45	356,3

Example 4

Preparation of compounds of formula I-D

The terephthalamide derivatives of formula I-D were prepared in an analogous manner to that described in the example 1.

no.	name	calc. MW (M+H)	found MW (M+H)
4-1	N-(2-amino-phenyl)-N'-(2-diisopropylamino-ethyl)-terephthalamide; ^{1}H-NMR (400 MHz, $(CH_3)_2SO$): δ = 9.77 (s, 1H), 8.54 (t, J = 5.3 Hz, 1H), 8.06 (m, 2H), 7.95 (m, 2H), 7.18 (m, 1H), 6.99 (m, 1H), 6.79 (m, 1H), 6.60 (m, 1H), 4.94 (s, 2H), 3.23 (m, 2H), 2.98 (m, 2H), 2.54 (t, J = 7.3 Hz, 2H), 0.99 (d, J = 6.6 Hz, 12H);	383.24	383.3
4-2	N-(2-amino-phenyl)-N'-(3-dibutylamino-propyl)-terephthalamide;	425.29	425.3
4-3	N-(2-amino-phenyl)-N'-(4-diethylamino-1-methyl-butyl)-terephthalamide;	397.26	397.2
4-4	N-(2-amino-phenyl)-N'-(3-diethylamino-propyl)-terephthalamide;	369.23	369.3
4-5	N-(2-amino-phenyl)-N'-(2-methoxy-1-methyl-ethyl)-terephthalamide;	328.17	328.2
4-6	N-(2-amino-phenyl)-N'-cyclopropylmethyl-terephthalamide;	310.16	310.2
4-7	N-(2-amino-phenyl)-N'-(3-ethoxy-propyl)-terephthalamide;	342.18	342.3
4-8	N-(2-amino-phenyl)-N'-(2-dimethylamino-ethyl)-terephthalamide;	327.18	327.3
4-9	N-(2-amino-phenyl)-N'-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-terephthalamide;	381.19	381.3
4-10	N-(2-amino-phenyl)-N'-(3-dimethylamino-2,2-dimethyl-propyl)-terephthalamide;	369.23	369.3
4-11	N-allyl-N'-(2-amino-phenyl)-terephthalamide;	296.14	296.2
4-12	N-(2-amino-phenyl)-N'-butyl-terephthalamide;	312.17	312.2
4-13	N-(2-amino-phenyl)-N'-butyl-N'-methyl-	326.19	326.3

no.	name	calc. MW (M+H)	found MW (M+H)
	terephthalamide.		

Example 5

Preparation of compounds of formula I-E

In analogy to steps 1 to 4 of Example 1 and using the corresponding starting materials the following compounds were prepared:

no.	name	calc. MW (M+H)	found MW (M+H)
5-1	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methoxy-amide),	292.08	292.2
5-2	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(ethoxy-amide),	306.09	306.1
5-3	thiophene-2,5-dicarboxylic acid 2-(allyloxy-amide) 5-[(2-amino-phenyl)-amide], H-NMR (400 MHz, $(CH_3)_2SO$): δ = 11.90 (s, 1H), 9.82 (s, 1H), 7.93 (m, 1H), 7.78 (m, 1H), 7.65 (m, 1H), 7.12 (m, 1H), 6.99 (m, 1H), 6.78 (m, 1H), 6.59 (m, 1H), 6.05-5.95 (m, 1H), 5.39-5.35 (m, 1H), 5.30-5.28 (m, 1H), 4.95 (s, 2H), 4.42 (d, J = 6.1 Hz, 1H),	318.09	318.2
5-4	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(phenoxy-amide),	354.09	354.2
5-5	pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-hydroxyamide, H-NMR (400 MHz, $(CH_3)_2SO$): δ = 11.61 (s, 1H), 10.12 (s, 1H), 9.36 (s, 1H), 9.02 (m, 1H), 8.35 (m, 1H), 8.21 (m, 1H), 7.47 (m, 1H), 6.97 (m, 1H), 6.83 (m, 1H), 6.66 (m, 1H), 4.94 (s, 2H),	273.10	273.2
5-6	pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-hydroxyamide,	273.10	273.1
5-7	pyridine-2,6-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 6-hydroxyamide,	273.10	273.1

no.	name	calc. MW (M+H)	found MW (M+H)
5-8	pyridine-2,4-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 4-hydroxyamide,	273.10	273.1
5-9	thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(tert-butoxy-amide).	334,41	334,2

Example 6

a) Tablet Formulation (Wet Granulation):

Item	Ingredients	mg/tablet			
1.	Compound of formula I or A	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure:

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

b) Capsule Formulation:

Item	Ingredients	mg/capsule			
1.	Compound of formula I or A	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure:

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

The effect of the compounds according to the invention may further be assessed by the following test:

Method

Male NMRI nu/nu-mice(n = 15 per group), aged 8-10 weeks, were subcutaneously injected with 5*106 PC-3 prostate carcinoma cells. On day 10, animals with tumor volumes of about 150 mm^3 were randomly assigned to treatment groups. The test compound was administered as a microsuspension in 7,5% Gelatine - 0,22% NaCl-Suspension with an application volume of 10 ml/kg based on actual body weights. Once daily oral treatment was performed from approximately day 10 to day 27 on a, 5-7 times per week treatment schedule.

The volume of the tumor is determined from the following equation:

Volume of a tumor = $1/2ab^2$, where "a" and "b" are the long and the short diameters of the tumor, respectively

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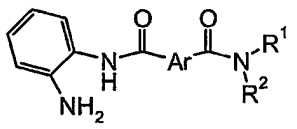
US 2,680,731
WO 93/21146

Patent Claims

1. Compounds of the general formula A



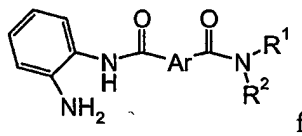
A

wherein

Ar		is thiophen-2,5-diyl, pyridine-2,5-diyl, pyridine-5,2-diyl, pyridine-2,6-diyl, pyridine-2,4-diyl or 1,4-phenylene,
R^1, R^2		independently from each other represent hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{3-12}-cycloalkyl, the alkyl, alkenyl, alkynyl and cycloalkyl groups being optionally mono or multiple substituted by hydroxy, halogen, C_{3-12}-cycloalkyl, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or -NR^3R^4, or alternatively
R^1		is hydrogen, and
R^2		is hydroxyl, alkoxy, C_2-C_{12}-alkenyloxy or phenoxy, which phenoxy group is optionally substituted with methyl, methoxy, halogen, nitro, cyano, trifluoromethyl, ethenyl or –C(O)-O-CH_3,
		provided that if R^2 is hydroxy, Ar is not thiophen-2,5-diyl; and
R^3 and R^4		independently from each other represent hydrogen or C_{1-6}-alkyl, or wherein
R^3 and R^4		together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom,

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1 of the general formula I



formula I

wherein

Ar	is thiophen-2,5-diyl, pyridine-2,5-diyl, pyridine-5,2-diyl or 1,4-phenylene,
R^1, R^2	independently from each other represent hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{3-12}-cycloalkyl, the alkyl, alkenyl, alkynyl and cycloalkyl groups being optionally mono or multiple substituted by hydroxy, halogen, C_{3-12}-cycloalkyl, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$,
R^3 and R^4	independently from each other represent hydrogen or C_{1-6}-alkyl, or wherein
R^3 and R^4	together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom,

and pharmaceutically acceptable salts thereof.

3. Compounds of formula I according to claim 2, wherein R^1 is hydrogen or alkyl, and R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined in claim 2.

4. Compounds of formula I according to claim 2, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl.

5. Compounds of formula I according to claim 2, wherein R^1 is hydrogen and R^2 is unsubstituted straight or branched C_{1-12}-alkyl or alkyl mono or multiple

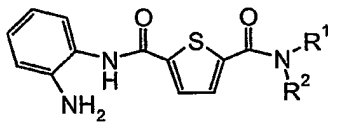
substituted by alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-.

6. Compounds of formula I according to claim 2, wherein R^1 is hydrogen and R^2 is C_{1-12}-alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl.

7. Compounds of formula I according to claim 2, wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom.

8. Compounds of formula I according to claim 2, wherein R^1 is hydrogen or alkyl and R^2 is cycloalkyl or alkyl substituted by cycloalkyl.

9. Compounds according to claim 2, wherein Ar is thiophen-2,5-diyl of the formula



I-A

wherein R^1 and R^2 are as defined in claim 2.

10. Compounds according to claim 9, wherein R^1 is hydrogen or C_{1-6}-alkyl; and R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined in claim 2.

11. The compounds according to claim 10

thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(butyl-methyl-amide),
thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-diethylamide,

Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-prop-2-ynyl-amide),
thiophene-2,5-dicarboxylic acid 2-(allyl-methyl-amide) 5-[(2-amino-phenyl)-amide],
thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylaminoethyl)-ethyl-amide],
thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-dipropylamide,
thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-pentyl-amide),
thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diethylaminoethyl)-methyl-amide],
thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[bis-(2-methoxy-ethyl)-amide], or
thiophene-2,5-dicarboxylic acid 2-amide 5-[(2-amino-phenyl)-amide].

12. The compounds according to claim 9, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl.

13. The compounds according to claim 12

thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-prop-2-ynylamide, or
thiophene-2,5-dicarboxylic acid 2-allylamide 5-[(2-amino-phenyl)-amide].

14. The compounds according to claim 9, wherein R^1 is hydrogen and R^2 is unsubstituted straight or branched C_{1-12}-alkyl or alkyl mono or multiple substituted by alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-.

15. The compounds according to claim 14

Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-butyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-hexyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-methoxy-propyl)-amide],

Thiophene-2,5-dicarboxylic acid 2-[(2-acetylaminoethyl)-amide] 5-[(2-amino-phenyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-ethyl-hexyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1,5-dimethyl-hexyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methoxy-1-methyl-ethyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-pentylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-butylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-ethoxy-propyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-sec-butylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-heptylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-nonylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-octylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-heptyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(isobutylamide),
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-propylamide, or
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methyl-butyl)-amide].

16. The compounds according to claim 9, wherein R^1 is hydrogen and R^2 is C_{1-12}-alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl.

17. Examples of such compounds are

Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-diethylamino-1-methyl-butyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-diethylamino-propyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dibutylamino-propyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dimethylaminopropyl)-amide],

Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-diisopropylaminoethyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dimethylamino-2,2-dimethylpropyl)-amide], or
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylaminoethyl)-amide].

18. The compounds according to claim 9, wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom.

19. The compound according to claim 18

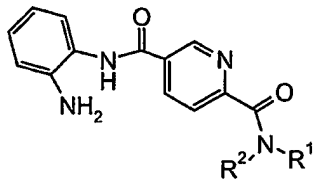
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-{[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide}.

20. The compounds according to claim 9, wherein R^1 is hydrogen or alkyl and R^2 is cycloalkyl or alkyl substituted by cycloalkyl.

21. The compounds according to claim 20

Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cycloheptylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclooctylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclopentylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclobutylamide,
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(cyclopropylmethyl-propyl-amide), or
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclopropylmethyl-amide.

22. The compounds according to claim 2, wherein Ar is pyridine-2,5-diyl of formula I-B



I-B,

wherein

R^1 is hydrogen or alkyl; and

R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined above.

23. The compounds according to claim 22

Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-(butyl-methyl-amide),
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-dipropylamide,
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-(methyl-pentyl-amide),
Pyridine-2,5-dicarboxylic acid 2-(allyl-methyl-amide) 5-[(2-amino-phenyl)-amide],
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[bis-(2-methoxy-ethyl)-amide], or
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-diethylaminoethyl)-methyl-amide].

24. The compounds according to claim 22, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl.

25. The compound according to claim 24

Pyridine-2,5-dicarboxylic acid 2-allylamide 5-[(2-amino-phenyl)-amide].

26. The compounds according to claim 22, wherein R^1 is hydrogen and R^2 is unsubstituted straight or branched C_{1-12}-alkyl or alkyl mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-.

27. The compounds according to claim 26

Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-hexylamide,
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-methoxy-ethyl)-amide],
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(3-butoxy-propyl)-amide],
{[5-(2-amino-phenylcarbamoyl)-pyridine-2-carbonyl]-amino}-acetic acid methyl ester,
3-{[5-(2-amino-phenylcarbamoyl)-pyridine-2-carbonyl]-amino}-propionic acid tert-butyl ester,
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2,2,3,3,3-pentafluoro-propyl)-amide],
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2,2,3,3,4,4,4-heptafluoro-butyl)-amide],
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(1,5-dimethyl-hexyl)-amide],
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(1-methyl-hexyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-acetylaminoethyl)-amide] 5-[(2-amino-phenyl)-amide].

28. The compounds according to claim 22, wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl.

29. The compounds according to claim 28

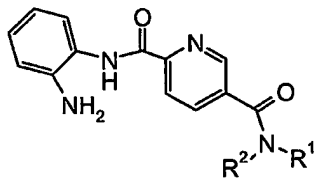
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-diisopropylamino-ethyl)-amide], or
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(3-dibutylamino-propyl)-amide].

30. The compounds according to claim 22, wherein R^1 is hydrogen and R^2 is cycloalkyl.

31. The compound according to claim 30

Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-cyclooctylamide.

32. The compounds according to claim 2, wherein Ar signifies pyridine-5,2-diyl of formula I-C



I-C,

wherein

R1 is hydrogen or alkyl; and

R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined above.

33. The compounds according to claim 32

pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(butyl-methyl-amide),
pyridine-2,5-dicarboxylic acid 5-(allyl-methyl-amide) 2-[(2-amino-phenyl)-amide],

pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-prop-2-ynyl-amide),
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[bis-(2-methoxyethyl)-amide],
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methyl-pentyl-amide),
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-dipropylamide,
or
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diethylaminoethyl)-methyl-amide].

34. The compounds according to claim 32, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl.

35. The compound according to claim 34

pyridine-2,5-dicarboxylic acid 5-allylamide 2-[(2-amino-phenyl)-amide].

36. The compounds according to claim 32, wherein R^1 is hydrogen and R^2 is unsubstituted alkyl or alkyl mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-.

37. The compounds according to claim 36

pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-hexylamide,
pyridine-2,5-dicarboxylic acid 5-[(2-acetylamino-ethyl)-amide] 2-[(2-amino-phenyl)-amide],
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2,2,3,3,3-pentafluoro-propyl)-amide],
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2,2,3,3,4,4,4-heptafluoro-butyl)-amide],
3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-butyric acid ethyl ester,
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-hydroxy-propyl)-amide],

2-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-3-methyl-butyric acid methyl ester,
3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-propionic acid ethyl ester,
{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-acetic acid methyl ester,
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-methoxy-ethyl)-amide],
2-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-4-methylsulfanyl-butyric acid methyl ester,
3-{[6-(2-amino-phenylcarbamoyl)-pyridine-3-carbonyl]-amino}-propionic acid tert-butyl ester,
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2,3-dihydroxy-propyl)-amide],
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-butoxy-propyl)-amide],
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-sec-butylamide,
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1,5-dimethyl-hexyl)-amide], or
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-methyl-hexyl)-amide].

38. The compounds according to claim 32, wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl.

39. The compounds according to claim 38

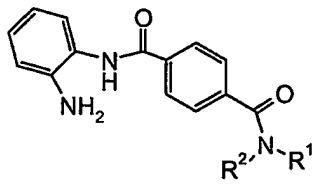
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-diisopropylamino-ethyl)-amide],
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylamino-ethyl)-amide],
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-diethylamino-1-methyl-butyl)-amide], or
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(3-dibutylamino-propyl)-amide].

40. The compounds according to claim 32, wherein R^1 is hydrogen or alkyl and R^2 is cycloalkyl.

41. The compounds according to claim 40

pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-cyclooctylamide, or
pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(cyclopropylmethyl-propyl-amide).

42. The compounds according to claim 2, wherein Ar signifies 1,4-phenylene, of formula I-D



I-D,

wherein

R^1 is hydrogen or alkyl; and

R^2 is hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, the alkyl, alkenyl and alkynyl groups being optionally mono or multiple substituted by hydroxy, halogen, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$; wherein R^3R^4 are as defined above.

43. The compound according to claim 42

N-(2-amino-phenyl)-N'-butyl-N'-methyl-terephthalamide.

44. The compounds according to claim 42, wherein R^1 is hydrogen and R^2 is alkenyl or alkynyl.

45. The compound according to claim 44

N-allyl-N'-(2-amino-phenyl)-terephthalamide.

46. The compounds according to claim 42, wherein R^1 is hydrogen and R^2 is unsubstituted straight or branched alkyl or alkyl mono or multiple substituted by , alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, or C_{1-6}-alkyl-C(O)NH-.

47. The compounds according to claim 46

N-(2-amino-phenyl)-N'-(2-methoxy-1-methyl-ethyl)-terephthalamide,
N-(2-amino-phenyl)-N'-(3-ethoxy-propyl)-terephthalamide, or
N-(2-amino-phenyl)-N'-butyl-terephthalamide.

48. The compounds according to claim 42, wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl.

49. The compounds according to claim 48

N-(2-amino-phenyl)-N'-(2-diisopropylamino-ethyl)-terephthalamide,
N-(2-amino-phenyl)-N'-(3-dibutylamino-propyl)-terephthalamide,
N-(2-amino-phenyl)-N'-(4-diethylamino-1-methyl-butyl)-terephthalamide,
N-(2-amino-phenyl)-N'-(3-diethylamino-propyl)-terephthalamide,
N-(2-amino-phenyl)-N'-(2-dimethylamino-ethyl)-terephthalamide, or
N-(2-amino-phenyl)-N'-(3-dimethylamino-2,2-dimethyl-propyl)-terephthalamide.

50. The compounds according to claim 42, wherein R^1 is hydrogen and R^2 is alkyl mono or multiple substituted by $-NR^3R^4$, wherein R^3 and R^4 together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom.

51. The compound according to claim 50

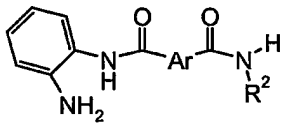
N-(2-amino-phenyl)-N'-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-terephthalamide.

52. The compounds according to claim 42, wherein R^1 is hydrogen, alkyl or alkenyl and R^2 is cycloalkyl or alkyl substituted by cycloalkyl.

53. The compound according to claim 52

N-(2-amino-phenyl)-N'-cyclopropylmethyl-terephthalamide.

54. The compounds according to claim 1, of the formula I-E



I-E

wherein

Ar is thiophen-2,5-diyl, pyridine-2,5-diyl, pyridine-2,6-diyl, pyridine-2,4-diyl, pyridine-5,2-diyl or 1,4-phenylene; and

R^2 represents hydroxyl, alkoxy, C_2-C_{12}-alkenyloxy or phenoxy, provided that if R^2 is hydroxy, Ar is not thiophen-2,5-diyl.

55. The compounds according to claim 54

Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(methoxy-amide),
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(ethoxy-amide),
Thiophene-2,5-dicarboxylic acid 2-(allyloxy-amide) 5-[(2-amino-phenyl)-amide],
Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(phenoxy-amide),
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-hydroxyamide,
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-hydroxyamide,
Pyridine-2,6-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 6-hydroxyamide, or

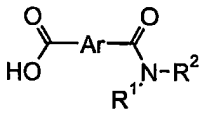
Pyridine-2,4-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 4-hydroxyamide.

56. The compounds according to claim 1 or 2

Thiophene-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-(tert-butoxy-amide),
Pyridine-2,5-dicarboxylic acid 2-(allyl-cyclopentyl-amide) 5-[(2-amino-phenyl)-amide],
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-(cyclopropylmethyl-propyl-amide),
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-sec-butylamide,
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-hydroxy-ethyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-{[2-(2-hydroxy-ethoxy)-ethyl]-amide},
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-cyclohexylmethyl-2-hydroxy-ethyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-hydroxy-butyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(1-hydroxymethyl-2-methyl-butyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(4-hydroxy-cyclohexyl)-amide],
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-({2-[bis-(2-hydroxy-ethyl)-amino]-ethyl}-amide),
Pyridine-2,5-dicarboxylic acid 5-[(2-amino-phenyl)-amide] 2-[(2-dimethylamino-ethyl)-amide] or
Pyridine-2,5-dicarboxylic acid 2-[(2-amino-phenyl)-amide] 5-[(2-dimethylamino-ethyl)-ethyl-amide].

57. A process for the preparation of compounds according to any one of claims 1 to 56 characterized in that

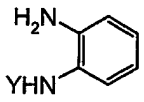
(1) a compound of the formula II



II

wherein Ar, R^1 and R^2 are as defined in claim 1, and R^2 might carry a protecting group to prepare the compounds wherein R^2 is hydroxy;

is reacted with a compound of the formula III



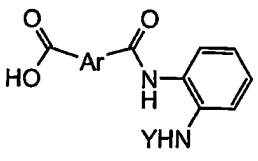
III

wherein Y represents hydrogen or a suitable amino protecting group;

by first activating the compound of formula II in the presence of an activating agent and subsequently adding the the compound of formula III, finally cleaving off the protecting groups where necessary;

or

(2) a compound of the formula VI



VI

wherein Ar is as defined in claim 1 and Y is suitable protecting group as described in (1)

is reacted with an an amine of the formula HNR^1R^2 in which R^1 and R^2 are as defined in claim 1, and R^2 might also carry a protecting group to prepare the compounds wherein R^2 is hydroxy, and finally cleaving off the protecting groups where necessary;

and

(3) if desired, transforming the product into a pharmaceutically acceptable salt by addition of a suitable acid or base.

58. A medicament containing one or more compounds as claimed in any one of claims 1 to 56 and pharmaceutically acceptable excipients.

59. A medicament according to claim 58 for the inhibition of tumor growth.

60. The use of a compound in any one of claims 1 to 56 for the treatment of cancer.

61. The use of a compound in any one of claims 1 to 56 for the manufacture of corresponding medicaments for the inhibition of tumor growth.

62. A medicament according to claim 58 for the treatment of cancer.

63. A method for inhibiting tumor growth by contacting said tumor cell with an effective amount of one or more compounds according to one of the claims 1 to 56.

64. A compound according to any of the claims 1 to 56, whenever prepared by a process as claimed in claim 57 or by an equivalent method.

65. The invention as hereinbefore described.

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(71) Applicant: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(72) Inventors: **FERTIG, Georg**; Wolfbauerweg 6, 82377 Penzberg (DE). **HERTING, Frank**; Frauenschuhstrasse 38, 82377 Penzberg (DE). **KUBBIES, Manfred**; Glaswandstrasse 7c, 82377 Penzberg (DE). **LIMBERG, Anja**; Würmseestrasse 58, 81476 München (DE). **REIFF, Ulrike**; Weidenweg 6, 82377 Penzberg (DE). **WEIDNER, Michael**; Ludwig-März-Strasse 39a, 82377 Penzberg (DE).

(74) Agent: **SCHREINER, Siegfried**; Roche Diagnostics GmbH, Patent Department (TR-E), Postfach 11 52, 82372 Penzberg (DE).

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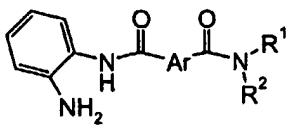
(54) Title: MONO-ACYLATED O-PHENYLENDIAMINES DERIVATIVES AND THEIR USE AGAINST CANCER



A

(57) Abstract: Objects of the present invention are new mono-acylated o-phenylendiamines derivatives of formula (A) wherein Ar is thiophen-2,5-diyl, pyridine-2,5-diyl, pyridine-5,2-diyl, pyridine-2,6-diyl, pyridine-2,4-diyl or 1,4-phenylene, R^1, R^2 independently from each other represent hydrogen, C_{1-12}-alkyl, C_{2-12}-alkenyl, C_{2-12}-alkynyl, C_{3-12}-cycloalkyl, the alkyl, alkenyl, alkynyl and cycloalkyl groups being optionally mono or multiple substituted by hydroxy, halogen, C_{3-12}-cycloalkyl, alkoxy, alkylsulfanyl, acyloxy, alkoxycarbonyl, acyl, C_{1-6}-alkyl-NH-C(O)-, C_{1-6}-alkyl-C(O)NH- or $-NR^3R^4$, or alternatively R^1 is hydrogen, and R^2 is hydroxyl, alkoxy, C_2-C_{12}-alkenyloxy or phenoxy, which phenoxy group is optionally substituted with methyl, methoxy, halogen, nitro, cyano, trifluoromethyl, ethenyl or $-C(O)-O-CH_3$, provided that if R^2 is hydroxy, Ar is not thiophen-2,5-diyl; and R^3 and R^4 independently from each other represent hydrogen or C_{1-6}-alkyl, or wherein R^3 and R^4 together with the nitrogen-atom to which they are attached form a ring, which ring is monosubstituted by oxo and which ring may contain a further heteroatom, and pharmaceutically acceptable salts thereof, as well as processes for the manufacturing of these compounds, pharmaceutical compositions containing such compounds and their use in the manufacture of drugs for the treatment of diseases such as cancer.

WO 2004/069803 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001044

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/90 A61K31/381 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/013757 A1 (SATTELKAU TIM ET AL) 16 January 2003 (2003-01-16) claim 1	1-21, 54-65
A	EP 0 847 992 A (MITSUI CHEMICALS INC) 17 June 1998 (1998-06-17) cited in the application page 1, lines 1-5; claim 1	1-21, 54-65
A	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 14, 31 December 1998 (1998-12-31) & JP 10 259176 A (JAPAN TOBACCO INC), 29 September 1998 (1998-09-29) abstract	1-21, 54-65

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 July 2004	30. 09. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Samsam Bakhtiary, M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001044

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 137 918 A (WEIERSHAUSEN UTE ET AL) 11 August 1992 (1992-08-11) claim 1	1-21, 54-65
A	PICARD, CLAUDE ET AL: "Desymmetrization reactions: a convenient synthesis of aromatic diamide diamines" SYNTHESIS (2001), (10), 1471-1478, 2001, XP001097260 page 1473 scheme 2	1-21, 54-65

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/001044

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 63 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 63 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/001044

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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